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Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre

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Cerebrovascular disease and vascular risk factors are associated with Alzheimer's disease, but the evidence for their association with other neurodegenerative disorders is limited. Therefore, we compared the prevalence of cerebrovascular disease, vascular pathology and vascular risk factors in a wide range of neurodegenerative diseases and correlate them with dementia severity. Presence of cerebrovascular disease, vascular pathology and vascular risk factors was studied in 5715 cases of the National Alzheimer's Coordinating Centre database with a single neurodegenerative disease diagnosis (Alzheimer's disease, frontotemporal lobar degeneration due to tau, and TAR DNA-binding protein 43 immunoreactive deposits, α-synucleinopathies, hippocampal sclerosis and prion disease) based on a neuropathological examination with or without cerebrovascular disease, defined neuropathologically. In addition, 210 'unremarkable brain' cases without cognitive impairment, and 280 cases with pure cerebrovascular disease were included for comparison. Cases with cerebrovascular disease were older than those without cerebrovascular disease in all the groups except for those with hippocampal sclerosis. After controlling for age and gender as fixed effects and centre as a random effect, we observed that α-synucleinopathies, frontotemporal lobar degeneration due to tau and TAR DNA-binding protein 43, and prion disease showed a lower prevalence of coincident cerebrovascular disease than patients with Alzheimer's disease, and this was more significant in younger subjects. When cerebrovascular disease was also present, patients with Alzheimer's disease and patients with α-synucleinopathy showed relatively lower burdens of their respective lesions than those without cerebrovascular disease in the context of comparable severity of dementia at time of death. Concurrent cerebrovascular disease is a common neuropathological finding in aged subjects with dementia, is more common in Alzheimer's disease than in other neurodegenerative disorders, especially in younger subjects, and lowers the threshold for dementia due to Alzheimer's disease and α-synucleinopathies, which suggests that these disorders should be targeted by treatments for cerebrovascular disease.

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Abbreviations: CERAD = Consortium to Establish A Registry of Alzheimer's disease; FTLD = frontotemporal lobar degeneration; NACC = National Alzheimer's Coordinating Centre

Introduction

Alzheimer's disease is the most common cause of dementia in the general population, followed by vascular dementia, α-synucleinopathies (including dementia with Lewy bodies, Parkinson's disease dementia) and frontotemporal lobar degeneration (FTLD) due to tau immunoreactive inclusions (FTLD-Tau) and TAR DNA binding protein 43 immunoreactive inclusions (FTLD-TDP). With age there is an increasing prevalence of coincident Alzheimer's disease and cerebrovascular disease that is well-recognized. Alzheimer's disease has been reported to present frequently together with microscopic cerebrovascular lesions (Jellinger and Attems, 2010). Cerebrovascular disease has been previously associated with worse cognitive performance in Alzheimer's disease and neuropathological studies report that cerebrovascular disease lowers the threshold for dementia in subjects with a neuropathological diagnosis of Alzheimer's disease (Snowdon *et al.*, 1997; Chui *et al.*, 2006; De Reuck *et al.*, 2012; Bennett *et al.*, 2013). In addition, epidemiological studies have shown that Alzheimer's disease and cerebrovascular disease not only share age as a risk factor, but also vascular risk factors have been linked to Alzheimer's disease and are among the most important modifiable risk factors for Alzheimer's disease (Kling *et al.*, 2013). Cerebrovascular disease has been suggested to contribute to Alzheimer's disease neuropathological changes including selective brain atrophy and accumulation of abnormal proteins such as amyloid-β (Zlokovic, 2011; Kalaria *et al.*, 2012; Toledo *et al.*, 2012*a*). Indeed, atherosclerosis in the circle of Willis has been specifically linked to Alzheimer's disease, but not to a diverse range of other common or rare neurodegenerative diseases (Roher *et al.*, 2011; Yarchoan *et al.*, 2012).

Few studies have investigated the association between cerebrovascular disease and other neurodegenerative diseases such as α-synucleinopathies (Jellinger, 2003; Jellinger and Attems, 2008, 2011; Ghebremedhin *et al.*, 2010; Schwartz *et al.*, 2012) or FTLD (De Reuck *et al.*, 2012) and findings have been inconsistent. No study has compared the presence of cerebrovascular disease across the whole spectrum of neurodegenerative diseases. The degree to which comorbid cerebrovascular disease modifies or otherwise affects the correlation of neurodegenerative disease pathology with a disease's clinical diagnosis and features is less studied in these neurodegenerative diseases.

To begin to address the question of the differential contribution of cerebrovascular disease to Alzheimer's disease and other cerebrovascular diseases, we interrogated the National Alzheimer's Coordinating Centre (NACC) database cases with autopsy-based neuropathological diagnosis (Beekly *et al.*, 2004). Specifically, we: (i) ascertained the concurrence of cerebrovascular disease diagnosis (established based on the neuropathological examination) or the presence of vascular pathology not meeting the threshold for a diagnosis of cerebrovascular disease in the different neurodegenerative disease groups using adjusted multivariable models in the whole sample; (ii) compared the presence of vascular risk factors in the different neurodegenerative disease groups in the whole sample; and (iii) correlated the presence of cerebrovascular disease in the different neurodegenerative disease with clinical data in their last visit.

Materials and methods

Study subjects

The NACC was established by the National Institute on Ageing (U01 AG016976) in 1999 to facilitate collaborative research. The NACC collects data from 35 past and present National Institute of Ageing funded Alzheimer's disease Centres across the USA. For this study neuropathological data were gathered from the NACC Neuropathology Data Set (Beekly *et al.*, 2004) and clinical data associated with these cases were gathered from both the NACC Minimum Data Set (Weintraub *et al.*, 2009) and the NACC Uniform Data Set (Beekly *et al.*, 2007) in collaboration with NACC personnel (S.E.M., W.A.K.). The Minimum Data Set was implemented in 1999 and contains information on demographics, selected clinical manifestations, clinical diagnoses, and neuropathological diagnoses. The Uniform Data Set superseded the Minimum Data Set in 2005, continuing to follow still living and active cases in the Minimum Data Set, recruiting new cases, and accruing more extensive information than the Minimum Data Set, including neurological examination findings, functional status, neuropsychological test results and genetic information. Our analysis was performed using data from the September 2012 freeze of these data sets. More detailed information on the NACC database can be found online (http://www.alz.washington.edu/).

The initial data pull included 12 738 subjects. Only subjects with a single neurodegenerative disease were selected to be able to compare the coincidence of cerebrovascular disease, and specific vascular lesions in each of the neurodegenerative diseases. From these, 6205 subjects were included and assigned into one of eight neuropathological diagnostic categories for the final analysis: (i) Alzheimer's disease ($n = 4629$); (ii) FTLD-Tau ($n = 379$); (iii) FTLD-TDP43 ($n = 207$); (iv) α-synucleinopathies ($n = 323$); (v) hippocampal sclerosis ($n = 77$); (vi) prion disease ($n = 100$); (vii) unremarkable brain ($n = 210$); and (viii) cerebrovascular disease ($n = 280$). Subjects ($n = 6533$) were excluded for the following reasons: (i) neuropathological diagnosis could not be assessed accurately ($n = 1025$); (ii) the underlying disorders were rare diseases in this database (e.g. Huntington's disease, neuronal intermediate filament inclusion disease) that could not be constituted into a group for statistical analyses ($n = 64$); (iii) non- neurodegenerative disease conditions (e.g. CNS lymphoma, Wernicke-Korsakoff, $n = 43$); (iv) cases that were not considered neuropathologically normal, but had insufficient Alzheimer's disease pathology to establish a diagnosis ($n = 160$); (v) incidental Lewy bodies ($n = 62$); (vi) diagnosis was dementia lacking distinct histology ($n = 144$); (vii) subjects diagnosed with unremarkable (normal) brain but who had cognitive impairment or dementia ($n = 54$); (viii) had been studied before 1997 [$n = 2393$, pre-National Institute of Ageing-Reagan criteria (1997) and α-synuclein (Baba *et al.*, 1998)

era]; and (ix) multiple co-morbid pathologies, none of which could be assigned unequivocally as the predominant cause of the dementia ($n = 2588$). The α-synucleinopathy group included cases with dementia with Lewy bodies, Parkinson's disease dementia, Parkinson's disease and multiple system atrophy. The FTLD-Tau group included Pick's disease, corticobasal degeneration, progressive supranuclear palsy, tangle predominant senile dementia, argyrophilic grain disease and unclassifiable FTLD-Tau disorders. The FTLD-TDP group included demented subjects with and without motor neuron disease and amyotrophic lateral sclerosis cases. Finally, cases with unremarkable brain (without cognitive impairment) and cerebrovascular disease were included as negative and positive control groups, respectively, for comparison purposes. The counts/scores of each of the different neuropathological diagnoses within the FTLD-Tau, FTLD-TDP and α-synucleinopathy groups are detailed in Supplementary Table 1.

Two categories for vascular pathology data were available: (i) cerebrovascular disease, in which vascular pathology was classified as a primary or contributing neuropathology (Items 20E1–20E2 in the Neuropathology Data Set); and (ii) vascular pathology (Item 12), in which vascular pathologies were recorded independently of reaching or not a threshold deemed sufficient to contribute to clinical status. Therefore, the vascular pathology category encompasses a wider range of vascular changes and includes the group of cerebrovascular disease cases that represent a more severe stage. Vascular pathologies included large infarcts, multiple microinfarcts, lacunes, subcortical arteriosclerotic leukoencephalopathy and haemorrhages that were coded as present or absent (items 12A–E). Atherosclerosis in the circle of Willis, arteriolosclerosis and cerebral amyloid angiopathy were semi-quantitatively graded as none, mild, moderate and severe (12H–J). For analytical purposes these were collapsed into two categories: none/mild and moderate/severe. For Alzheimer's disease cases, Braak staging (Braak *et al.*, 2006) and Consortium to Establish A Registry of Alzheimer's disease (CERAD) amyloid plaque scores for likelihood of Alzheimer's disease (Mirra, 1997) were available. Brainstem, limbic and neocortical staging was available for α-synucleinopathy cases. All the clinical diagnoses are entered in the database using standardized fields. The criteria that the neuropathologists used to determine the existence of vascular features are described in the Neuropathology Guidebook (https://www.alz.washington.edu/NONMEMBER/NP/npguide9.pdf).

Data on vascular risk factors, which were obtained by the physician, were available only for subjects in the Uniform Data Set ($n = 1341$) and included hypertension, diabetes, hyperlipidaemia, tobacco use and known histories of cardiovascular disease or clinically defined cerebrovascular disease. These vascular risk factors were coded as unknown, absent, recent/active or remote/inactive. For analytical purposes, active and inactive categories were joined and compared to the absent category. A patient was considered to have coronary heart disease if he or she had a history of any of the following: heart attack, angioplasty/endarterectomy/stent or cardiac bypass procedure.

Statistical analysis

For the comparison of the demographic characteristics of the different neurodegenerative disease groups a Fisher exact test with Monte Carlo simulation was applied (instead of a chi-square test, because in certain analyses the expected cell count was low) (Agresti, 2002), whereas a percentile bootstrap method for comparing trimmed means was applied to assess quantitative variables due to heteroscedasticity associated with varying sample sizes in the different groups (Wilcox, 2012). The association between the different neurodegenerative diseases and the presence of cerebrovascular disease, vascular pathology, vascular risk factors, and dementia were studied in separate age- and gender-adjusted mixed effects logistic regression models that included the different Alzheimer's disease centres as a random effect to adjust for possible centre variability (Pinheiro and Bates, 2000). These models had Alzheimer's disease as the reference category so that the other diagnostic neurodegenerative disease groups were compared to Alzheimer's disease. To assess if the presence of cerebrovascular disease was associated with Braak stage in patients with Alzheimer's disease and the extent of Lewy body pathology in α-synucleinopathy cases, a binomial logistic regression model adjusted for age at death was applied. The association between the clinical dementia rating sum of boxes and the pathological features was studied using a linear regression model. For the dimensionality reduction of the pathological features a multiple factor analysis was used that allowed us to consider the binary categorical variables and the ordinal variables adequately (Bécue-Bertaut and Pagès, 2008). All analyses were conducted in R 2.15.2.

Results

Demographic differences between groups in the NACC Minimum Data Set database

The neuropathologically diagnosed neurodegenerative disease groups differed with respect to age at death, education, gender, race, APOE genotype, disease duration, age of onset of cognitive symptoms, prevalence of cerebrovascular disease and vascular pathology (Table 1). Cases with coincident cerebrovascular disease or vascular pathology were significantly older in all the neurodegenerative disease groups except the hippocampal sclerosis cases with cerebrovascular disease who showed no age differences when compared to hippocampal sclerosis subjects without cerebrovascular disease (Supplementary Table 2). Subjects with coincident cerebrovascular disease were 4–6 years older in the Alzheimer's disease and the α-synucleinopathy groups at time of death compared to those without cerebrovascular disease or vascular pathology, but the age difference increased to 10–19 years in the FTLD and prion groups with cerebrovascular disease.

Prevalence of cerebrovascular disease and vascular pathology in the different neurodegenerative disease groups

Alzheimer's disease showed a higher coincidence of vascular pathology and cerebrovascular disease (this category represents a subset of the vascular pathology category) than all the other studied disease groups except hippocampal sclerosis in the age, gender (fixed effects) and research centre (random effect) adjusted model (Fig. 1 and Table 2). We then studied if differences in cerebrovascular disease coincidence between Alzheimer's disease and the other neurodegenerative disease varied with age. We divided the sample in two groups based on a 73 years cut-off (median age of the non-Alzheimer's disease group) and found a significant interaction between age group and the

Table 1 Demographics of the NACC Minimum Data Set sample

	Alzheimer's disease	FTLD-Tau	FTLD-TDP	α-Synucleinopathy	Hippocampal sclerosis	Prion	Unremarkable brain	Cerebrovascular disease	*P*-value
Number of cases	4629	379	207	323	77	100	210	280	
Age at death, years	81.1 (10.4)	73.7 (12.0)	66.8 (10.3)	77.9 (9.5)	86.5 (10.8)	61.8 (11.4)	83.1 (9.5)	84.2 (8.2)	0.0001
Gender, % male	44.5	55.7	56.2	73.1	41.6	52.0	48.1	50.3	0.0005
APOE ε4, %	56.4	23.8	28.3	34.1	18.9	14.3	16.9	19.6	0.0005
Demented, %	85.7	89.0	83.7	80.5	67.5	91.7	0	44.3	0.0005
Cerebrovascular disease, %	32.3	17.3	5.2	20.2	39.2	4.8	–	100	<0.0001
Vascular pathology, %	79.9	64.7	60.9	66.2	84.9	41.3	67.3	100	0.0005
Large infarcts, %	12.7	5.4	3.6	8.3	17.9	1.3	10.0	28.3	0.0005
Lacunes, %	19.9	12.5	5.7	15.0	34.3	2.6	16.1	46.3	0.0005
Multiple microinfarcts, %	20.1	8.4	6.8	12.2	32.8	3.8	17.5	39.6	0.0005
Arteriosclerotic leukoencephalopathy, %	9.3	11.1	11.8	7.7	13.0	1.2	2.0	18.1	0.0005
Haemorrhages, %	6.8	3.0	3.0	4.8	4.4	0	4.0	11.8	0.0005
Atherosclerosis, %	39.8	25.2	20.5	27.0	50.7	6.3	22.6	51.5	0.0005
Arteriolosclerosis, %	34.6	35.2	18.1	28.8	46.8	7.7	10.3	54.8	0.0005
Cerebral amyloid angiopathy, %	40.8	7.2	9.2	11.9	10.5	4.1	10.7	9.1	0.0005

Data represent percentage or mean (standard deviation).

non-Alzheimer's disease neurodegenerative disease group [odds ratio (OR) = 0.62, $P = 0.013$], indicating comparatively lower prevalence of cerebrovascular disease in the younger non-Alzheimer's disease group, than in the older non-Alzheimer's disease when compared to the Alzheimer's disease group. α-Synucleinopathy, FTLD-Tau and FTLD-TDP did not show any difference in vascular pathology or cerebrovascular disease when compared to each other.

Finally, we compared the prevalence of the different vascular changes in the different diseases in the adjusted model, comparing Alzheimer's disease against the other groups finding several statistically significant results (Table 3). When Alzheimer's disease was compared with the FTLD-Tau and -TDP groups, Alzheimer's disease showed a higher prevalence of large and multiple microinfarcts than both groups of FTLD. In addition, Alzheimer's disease showed a higher prevalence of lacunes and moderate to severe arteriolosclerosis than FTLD-TDP and a higher prevalence of arteriosclerotic leukoencephalopathy, haemorrhages and moderate to severe atherosclerosis than FTLD-Tau. When compared to the α-synucleinopathy group the Alzheimer's disease group showed a higher prevalence of multiple microinfarcts and moderate to severe atherosclerosis and arteriolosclerosis. Prevalence of moderate to severe atherosclerosis and arteriolosclerosis and arteriosclerotic leukoencephalopathy was also higher in patients with Alzheimer's disease than the unremarkable brain. On the other hand, the hippocampal sclerosis showed a higher prevalence of arteriosclerotic leukoencephalopathy than the Alzheimer's disease group. The cerebrovascular disease group showed a higher prevalence of all the vascular pathology than Alzheimer's disease group, except for cerebral amyloid angiopathy, which was higher in the Alzheimer's disease group. Finally, Alzheimer's disease showed higher prevalence of moderate to severe cerebral amyloid angiopathy than all of the other groups. The prevalence of vascular changes in the vascular pathology group without cerebrovascular disease and the cerebrovascular disease groups (independently of the presence of a neurodegenerative disease) is summarized in Supplementary Table 3.

Association of cerebrovascular disease with disease burden

Two neurodegenerative disease groups, Alzheimer's disease and α-synucleinopathy groups, had data regarding their staging. Braak staging was available for Alzheimer's disease, and α-synucleinopathies were classified as brainstem, limbic/transitional, and neocortical stages. At time of death, demented subjects with a neuropathological diagnosis of Alzheimer's disease who had coincident cerebrovascular disease had lower Braak stages (I-IV versus V: OR = 0.44, $P < 0.0001$; I-IV versus VI: OR = 0.41, $P < 0.0001$) than those without cerebrovascular disease (OR = 0.42, $P < 0.0001$) (Fig. 1C) in an age-adjusted analysis. In addition, the presence of cerebrovascular disease also was associated with a trend for lower prevalence of Lewy body neocortical pathology in the α-synucleinopathy demented patients with cerebrovascular disease pathology (brainstem versus neocortical: OR = 0.30, $P = 0.059$) but not for limbic Lewy body disease (brainstem versus limbic: OR = 0.54, $P = 0.36$).

Association of cerebrovascular disease with dementia status and severity proximal to death

We investigated whether the presence of cerebrovascular disease increased the probability of being demented at the time of death. In the age and gender adjusted model, Braak neurofibrillary tangle staging was the strongest neuropathological predictor for dementia in subjects with a neuropathological diagnosis of Alzheimer's disease (stage VI versus stage I–IV: OR = 16.9, $P < 0.0001$; stage V versus stage I–IV: OR = 6.5, $P < 0.0001$), followed by the CERAD (CERAD

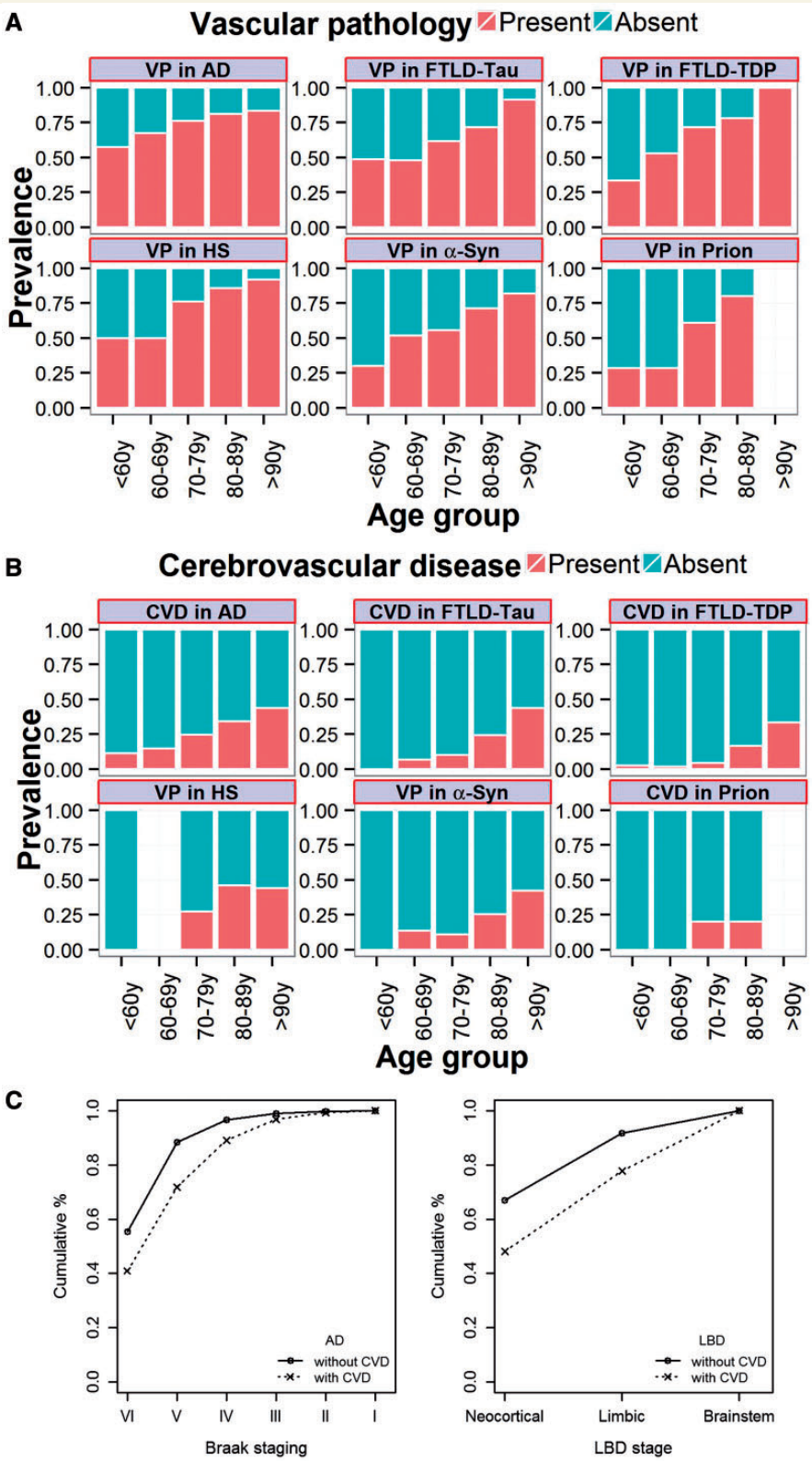

Figure 1 Prevalence of vascular pathology (**A**) and cerebrovascular disease (**B**) in the different neuropathologically diagnosed groups, and Braak stage (**C** *left*) and Lewy body disease stage (LBD; **C** *right*) stratified by the presence of cerebrovascular disease. AD = Alzheimer's disease; CVD = cerebrovascular disease; HS = hippocampal sclerosis; y = years.

Table 2 Comparison of vascular pathology and cerebrovascular disease prevalence in the different groups compared to Alzheimer's disease

Reference category for analysis	Analysed category	OR (95% confidence interval) for vascular pathology	*P*-value for vascular pathology	OR (95% confidence interval) for cerebrovascular disease	*P*-value for cerebrovascular disease
Alzheimer's disease	FTLD-Tau	0.37 (0.28–0.50)	<0.0001	0.38 (0.25–0.57)	<0.0001
Alzheimer's disease	FTLD-TDP	0.40 (0.28–0.58)	<0.0001	0.20 (0.09–0.42)	<0.0001
Alzheimer's disease	Hippocampal sclerosis	1.37 (0.64–2.98)	0.41	1.10 (0.59–2.04)	0.76
Alzheimer's disease	α-Synucleinopathy	0.38 (0.28–0.52)	<0.0001	0.47 (0.31–0.70)	0.0002
Alzheimer's disease	Prion disease	0.13 (0.08–0.23)	<0.0001	0.24 (0.07–0.83)	0.024
Alzheimer's disease	Unremarkable Brain	0.49 (0.39–0.61)	<0.0001	–	–
α-Synucleinopathy	FTLD-TDP	1.16 (0.71–1.91)	0.56	0.47 (0.19–1.17)	0.11
α-Synucleinopathy	FTLD-Tau	0.96 (0.63–1.45)	0.85	0.75 (0.42–1.35)	0.34
FTLD-TDP	FTLD-Tau	0.84 (0.53–1.33)	0.46	0.84 (0.53–1.33)	0.46

Table 3 Differences in vascular changes in Alzheimer's disease compared to the different groups in the analysis adjusted for age at death and gender

Variable	FTLD-Tau	FTLD-TDP	α-Synucleinopathy	Hippocampal sclerosis	Prion	Unremarkable brain	Cerebrovascular disease
Large infarcts	2.0 (0.006)	2.3 (0.036)	1.4 (0.10)	0.9 (0.79)	–[a]	1.5 (0.12)	0.42 (<0.0001)
Multiple microinfarcts	2.4 (<0.0001)	2.4 (0.004)	2.0 (0.0006)	0.6 (0.79)	–[a]	1.5 (0.06)	0.4 (<0.0001)
Lacunes	1.3 (0.17)	2.3 (0.01)	1.3 (0.19)	0.7 (0.19)	–[a]	1.5 (0.05)	0.4 (<0.0001)
Arteriosclerotic leukoencephalopathy	1.6 (0.07)	1.5 (0.20)	1.1 (0.74)	0.3 (0.004)	–[a]	5.5 (0.003)	0.2 (<0.0001)
Haemorrhage	2.1 (0.03)	1.9 (0.15)	1.4 (0.26)	1.9 (0.30)	–[a]	1.8 (0.10)	0.6 (0.022)
Atherosclerosis	1.4 (0.02)	1.2 (0.38)	1.4 (0.01)	1.0 (0.89)	4.0 (0.004)	2.8 (<0.0001)	0.7 (0.006)
Arteriolosclerosis	1.3 (0.13)	2.4 (0.0001)	1.6 (0.005)	0.7 (0.22)	4.8 (0.0005)	3.6 (<0.0001)	0.4 (<0.0001)
Cerebral amyloid angiopathy	12.4 (<0.0001)	9.2 (<0.0001)	6.6 (<0.0001)	9.1 (<0.0001)	20.0 (<0.0001)	6.2 (<0.0001)	7.2 (<0.0001)

Data are represented as OR (*P*-values).
[a]This disease presented a low prevalence of changes and/or small sample size and could not be studied in the logistic regression model.

C versus CERAD A–B: OR = 2.0, $P < 0.0001$), and the presence of cerebrovascular disease (OR = 1.90, $P = 0.001$). Interestingly there was an interaction between cerebrovascular disease and Braak staging indicating that the association between cerebrovascular disease and dementia was lower in cases with higher Braak stage (for Braak VI: OR = 0.44, $P = 0.029$; for Braak V: OR = 0.48, $P = 0.049$). In the α-synucleinopathy group, the presence of neocortical Lewy bodies was the strongest neuropathological predictor of dementia (OR = 6.0, $P = 0.0001$), followed by the presence of cerebrovascular disease (OR = 3.8, $P = 0.029$), but there was no interaction between the Lewy body stage and the presence of cerebrovascular disease ($P = 0.11$). Clinical dementia rating sum of boxes scores within 2 years of death were available for 715 subjects with Alzheimer's disease (median = 8.3, first quartile = 4.7 months, third quartile 13.5 months) and 76 subjects with α-synucleinopathy (median = 8.2 months, first quartile = 4.0 months, third quartile = 12.1 months). Braak stage ($P < 0.0001$), CERAD score ($P < 0.0001$), and cerebrovascular disease ($P = 0.011$) predicted the clinical dementia rating sum of boxes score in the patients with Alzheimer's disease in the model that was also adjusted for gender and age. Neither the Lewy body disease stage ($P = 0.084$), nor the presence of cerebrovascular disease ($P = 0.58$) showed an association with clinical dementia rating sum of boxes score in the α-synucleinopathy group. We further performed a multiple factor analysis and tested the first two components that accounted for 52.7% of the variability of the categorical variables (large infarcts, multiple microinfarcts, lacunes, arteriosclerotic leukoencephalopathy, haemorrhage) and the first component that accounted for 47.0% of the variability of the ordinal variables (atherosclerosis, arteriolosclerosis and cerebral amyloid angiopathy). Only the first component of the ordinal variables showed a significant association with clinical dementia rating sum of boxes (t = 3.7, $P = 0.0003$) indicating that increasing arteriolosclerosis and atherosclerosis was associated with worse clinical dementia rating sum of boxes.

Association of vascular risk factors and cardiovascular disease with the different disease groups

The NACC Uniform Data Set contained information about vascular risk factors and cardiovascular disease in 1341 subjects. The neurodegenerative disease groups differed in the presence of active/inactive versus absent coronary heart disease, atrial fibrillation and hypertension (Table 4). The only differences when compared with the Alzheimer's disease group in the age and gender adjusted

Table 4 Prevalence of vascular risk factors and cardiovascular disease

	Alzheimer's disease	FTLD-Tau	FTLD-TDP	α-Synucleinopathy	Hippocampal sclerosis	Prion	Unremarkable brain	Cerebrovascular disease	*P*-value
Number of cases	845	118	86	102	24	44	35	87	
Coronary heart disease, %	18.0	12.7	4.7	16.7	20.8	6.8	37.1	23.0	0.0008
Atrial fibrillation, %	13.7	8.5	3.5	17.6	20.8	2.3	22.8	26.7	0.0008
Hypertension, %	56.2	55.1	36.5	52.0	75.0	45.5	70.6	75.6	0.0008
Hypercholesterolaemia, %	47.4	45.1	35.3	45.5	45.8	43.2	51.4	46.5	0.65
Diabetes, %	12.2	8.5	8.1	10.8	16.7	13.6	20.0	14.9	0.61
Smoking history, %	44.2	56.1	42.9	46.5	62.5	39.0	58.8	49.4	0.13

model were a higher prevalence of active/inactive coronary heart disease in the unremarkable brain group ($P = 0.0047$), a lower prevalence of active/inactive coronary heart disease in the FTLD-TDP group ($P = 0.041$), a higher prevalence of active/inactive atrial fibrillation in the α-synucleinopathy ($P = 0.046$) and cerebrovascular disease ($P = 0.022$) groups and a higher prevalence of active/inactive hypertension in the cerebrovascular disease group ($P = 0.008$). For reference, prevalence of active vascular risk factors and cardiovascular disease is summarized in Supplementary Table 4.

Discussion

To our knowledge, this study of the association of vascular pathology and cerebrovascular disease with Alzheimer's disease and other neurodegenerative disease reports on the largest and most diverse group of subjects with a neuropathologically confirmed neurodegenerative disease examined to date, and our analysis of data on uncommon as well as common neurodegenerative disease is unique. There were three novel findings from the age and gender-adjusted models: (i) Alzheimer's disease has a significantly higher prevalence of vascular pathology than α-synucleinopathy, FTLD-Tau and -TDP, prion disease and unremarkable brain; (ii) Alzheimer's disease has a significantly higher prevalence of cerebrovascular disease than α-synucleinopathy, FTLD-Tau and -TDP, and prion disease, and this was more prevalent at younger ages (Fig. 1); and (iii) the presence of cerebrovascular disease is associated with an increased risk of dementia in patients with α-synucleinopathy in addition to the increased risk in Alzheimer's disease.

We found that cerebrovascular disease and vascular pathology increased with age, as expected and described previously (Jellinger and Attems, 2010; Nelson *et al.*, 2011*a*), and accordingly, all subjects with neurodegenerative disease with cerebrovascular disease were older than those without cerebrovascular disease (except in the hippocampal sclerosis group). This age difference was greater in neurodegenerative disease with earlier ages of onset, like FTLD and prion disease, indicating the importance of age as a risk factor for cerebrovascular disease. Interestingly, this study showed in a single large and comprehensive sample that α-synucleinopathy, FTLD-Tau and FTLD-TDP, and prion disease have a lower prevalence of cerebrovascular disease than Alzheimer's disease in an age- and gender-adjusted analysis and that the difference in prevalence was even greater in the younger age group.

There is a large body of literature regarding coincidence of cerebrovascular disease and Alzheimer's disease and its correlation with dementia (Snowdon *et al.*, 1997; Mungas *et al.*, 2001; Petrovitch *et al.*, 2005; Schneider *et al.*, 2007, 2009; Jellinger and Attems, 2010; Deramecourt *et al.*, 2012). It is interesting that we found the association was stronger in lower Braak stages, which was previously described in one study for subcortical vascular pathology (Chui *et al.*, 2006) and for cerebrovascular disease (Petrovitch *et al.*, 2005). Our study confirms the findings of previous reports on the prevalence of cerebrovascular disease in Alzheimer's disease and the additive or interactive deleterious effect of Alzheimer's disease pathology and cerebrovascular disease on cognition (Snowdon *et al.*, 1997; Chui *et al.*, 2006; Jellinger and Attems, 2010; Arvanitakis *et al.*, 2011; Bennett *et al.*, 2013), and adds further evidence on the effect of Alzheimer's disease pathology (mainly plaques and tangles) to produce clinical symptoms (Nelson *et al.*, 2007; Bennett *et al.*, 2013).

In our study we also found that cerebrovascular disease in α-synucleinopathy is associated with dementia and the effect size was greater than in the Alzheimer's disease sample. Whereas neocortical Lewy body disease, senile plaques and neurofibrillary tangles are recognized as contributors to dementia in Lewy body disease (Irwin *et al.*, 2012), neuropathological studies report conflicting results of lower (Ghebremedhin *et al.*, 2010; Schwartz *et al.*, 2012), no difference (Choi *et al.*, 2010) or higher cerebrovascular disease (Jellinger and Attems, 2008) in patients with Lewy body disease and there is limited neuropathological evidence regarding the impact of cerebrovascular disease on cognitive function in Lewy body disease which, at most, points to a small overall effect (Jellinger, 2012). These conflicting results also extend to the association with cognitive impairment in clinical studies with studies showing a higher burden of white matter hyperintensities in Parkinson's disease than cognitively normal subjects whereas other studies describe no differences (Bohnen and Albin, 2011; Gonzalez-Redondo *et al.*, 2012). Similar conflicting results have also been described for the association with cognitive outcomes (Beyer *et al.*, 2006; Dalaker *et al.*, 2009; Bohnen and Albin, 2011; Gonzalez-Redondo *et al.*, 2012). In our study we found that the presence of cerebrovascular disease is a predictor of dementia in α-synucleinopathy at time of death. The effect size was larger in the Lewy body disease than in the Alzheimer's disease group and this association was similar across different degrees of pathology, indicating that the impact of cerebrovascular disease pathology might be stronger in Lewy body disease than

in Alzheimer's disease and that in Lewy body disease the impact is still significant in subjects with diffuse neocortical Lewy bodies. Our results indicate that cerebrovascular disease has an additive effect increasing the risk of dementia in Alzheimer's disease, although the effect is more prominent in earlier stages. To our knowledge, there are only two publications (Baborie *et al.*, 2011; De Reuck *et al.*, 2012) that have described a low prevalence of vascular pathology in FTLD, but neither of these studies included other neurodegenerative disease groups for comparison. We were not able to study the association between cerebrovascular disease and FTLD because we had no measure of the burden of the disease specific pathologies in this group. In the multiple factor analysis we found that the variables that were significantly associated with the clinical dementia rating sum of boxes 1 year before death in patients with Alzheimer's disease were the atherosclerosis and arteriolosclerosis grading, two variables that reflect progressive accumulative vascular changes. Two previous studies have described a similar association; intracranial atherosclerosis has been associated with dementia (Dolan *et al.*, 2010; Roher *et al.*, 2011) and in a study by Yarchoan *et al*. (2012), a significant correlation was reported between large vessel atherosclerosis and neurodegenerative changes in a large cohort of cases with neurodegenerative diseases, suggesting a specific association with plaques and tangles in Alzheimer's disease. Variables that graded vascular changes in a binary fashion did not show an association with the clinical dementia rating sum of boxes. There might be several explanations such as the absence of a quantification of the changes, the insensitiveness of the clinical dementia rating sum of boxes to the subcortical dementia profile present in cerebrovascular disease, the inclusion of subdural haematomas in the haemorrhage group and some of the vascular changes might have caused the death of the patient and were not present in the last clinical visit. Although we found a significantly higher burden of cerebrovascular disease in Alzheimer's disease than in other neurodegenerative diseases, some recent clinical studies have challenged the idea of a higher burden of cerebrovascular disease in Alzheimer's disease (Marchant *et al.*, 2013), although this study mainly consisted of cognitively normal or mildly impaired subjects and was enriched for vascular risk factors.

We were not able to study the association between cerebrovascular disease and FTLD because we had no measure of the burden of the disease-specific pathologies in this group.

Furthermore, unremarkable brain cases, and all subjects with neurodegenerative disease, except for the hippocampal sclerosis cases, showed a lower prevalence of vascular pathology than the Alzheimer's disease cases. Only pure cerebrovascular disease cases showed a higher prevalence of the different vascular pathology than cases with Alzheimer's disease. This could be explained by Alzheimer's disease sharing the same vascular risk factors as cerebrovascular disease or by the interaction of both pathologies, which could favour their common coincident occurrence. These findings lend support to the hypothesis that there is a pathophysiological link between Alzheimer's disease and cerebrovascular disease (Kalaria *et al.*, 2012), but, more importantly, we show for the first time that an association with cerebrovascular disease is specific for Alzheimer's disease compared with other neurodegenerative diseases. Interestingly, hippocampal sclerosis showed no differences in the prevalence of vascular pathology and cerebrovascular disease when compared with Alzheimer's disease, favouring recent studies indicating a strong association with TARDBP deposits rather than cerebrovascular disease (Dickson *et al.*, 1994; Corey-Bloom *et al.*, 1997; Leverenz *et al.*, 2002; Nelson *et al.*, 2011*b*). Nevertheless, hippocampal sclerosis was the only disorder that showed higher prevalence of several of the studied vascular changes (Table 3), which merits further analysis in studies that specifically study age-matched cohorts of Alzheimer's disease, hippocampal sclerosis and unremarkable brain cohorts.

This study has several strengths, including the large size of the cohort, the extensive data sets on the subjects we analysed, including different types of vascular pathologies, the diverse range of neurodegenerative diseases examined and the multivariable analysis. Of particular note, the post-mortem neuropathological diagnosis in the FTLD, α-synucleinopathy and cerebrovascular disease groups is of special importance as clinical diagnoses are not as reliably predictive of the neuropathology underlying these disorders (Toledo *et al.*, 2012*b*). Clinical Alzheimer's disease, amyotrophic lateral sclerosis and Parkinson's disease diagnoses generally show a good clinicopathological correlation (Hughes *et al.*, 2001; Toledo *et al.*, 2012*b*), but clinical FTD syndromes and dementia with Lewy bodies are not as reliably predictive of the neuropathology underlying these disorders (Toledo *et al.*, 2012*b*). For instance, 40% of patients with clinically diagnosed FTD are found to have a neuropathological diagnosis of Alzheimer's disease on post-mortem examination (Beach *et al.*, 2012; Nelson *et al.*, 2012; Toledo *et al.*, 2012*b*). In addition, the clinical criteria for vascular dementia have low diagnostic sensitivity (Gold *et al.*, 1997, 2002; Bacchetta *et al.*, 2007). Therefore, studies based on clinical diagnoses in the absence of a neuropathologically confirmed diagnosis are subject to significant confounds. Recently, a staging system for cerebrovascular disease has been proposed (Deramecourt *et al.*, 2012).

Relative weaknesses of the study are also acknowledged. As noted above, it is unfortunate that vascular risk factors were not recorded in our study subjects earlier in their lifespan at middle age; those recorded in NACC reflect a lifetime history. Although the similar diagnostic neuropathological diagnostic criteria were used, each centre follows different diagnostic procedures; however, we included a random factor in the mixed-effects model analysis to adjust for this factor. Our cases were recruited in tertiary care centres and therefore may differ from community-based studies and the cross-sectional nature of autopsy studies prevents us from establishing when pathological changes may have started. Finally, most of the data available to us were qualitative or categorical and the analyses of the vascular risk factors might have been underpowered for the less represented categories (although this is the largest sample for these cases) and the study of the association between the neuropathological findings and the clinical dementia rating sum of boxes. Additional associations might have been discerned if continuous, quantitative scale data were available.

An implication of this study is that in the absence of any specific disease-modifying treatments for Alzheimer's disease in the near future, we urge, based on the high prevalence on cerebrovascular disease described in our data here, that aggressive management of

vascular risk factors and encouragement of healthy lifestyles in midlife may have benefit for Alzheimer's disease or α-synucleinopathy individuals at increased risk to become clinically symptomatic, and probably to those with other causes of cognitive impairment. Indeed, even those who already manifest the clinical features of Alzheimer's disease or α-synucleinopathy may benefit from effective therapies that mitigate vascular risk factors and cerebrovascular disease. Guidelines for treatment and prevention of vascular contributions to dementia are available (Gorelick *et al.*, 2011). Finally, we propose that it is timely to consider inclusion of patients with vascular risk factors, cardiovascular disease and cerebrovascular disease in clinical studies as these cases are often excluded currently, but they account for a large percentage of the subjects with dementia and thereby more accurately embody the challenges we must face in developing disease-modifying therapies for Alzheimer's disease.

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Supplementary material

Supplementary material is available at *Brain* online.

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